GABA ESTERS AND GABA ANALOG ESTERS

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation of application Ser. No. 06/767,903, filed Aug. 15, 1985, now abandoned, which application is a continuation-in-part of application Ser. No. 519,61, filed Aug. 1, 1983, now abandoned and Ser. No. 640,507, filed July 24, 1984, now abandoned.

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates to derivatives of gamma-aminobutyric acid (GABA) and to derivatives of gamma-aminobutyric acid analogues (GABA analogues), more particularly to ester derivatives of GABA and GABA analogues which cross the blood brain barrier, as well as to methods of synthesizing and using these compounds.

2. Description of the Background Art

GABA is an amino acid which has a ubiquitous distribution in the central nervous system (CNS) and fulfills the main criteria established for the identification of a neurotransmitter:

1. GABA is synthesized and selectively released from nerve terminals,
2. the release of GABA can be induced in vitro and in vivo,
3. exogenously-applied GABA mimics the inhibitory effects elicited after neuronal stimulation,
4. pre- and post-synaptic GABA receptors have been identified, and
5. membrane transport systems and processes for determination of the neurotransmission process and for the inactivation of GABA, have been characterized.

The variation of CNS levels of GABA has been linked to certain neurological and psychiatric diseases. Low levels of GABA and of the GABA-synthesizing enzyme glutamate decarboxylase have been measured in post mortem brain tissue from patients suffering from Huntington's chorea. In Parkinson's disease, there is an imbalance between the GABA and the dopamine systems. In some brain areas of Parkinsonian patients, GABA receptor density is below normal levels. Analysis of brain samples from sites near seizure foci in epileptics revealed reduced GABA uptake capacity, probably reflecting degeneration of GABA neurons. Further, decreased GABA activity found in autopsies of schizophrenics suggests that GABA is also involved in the pathophysiology of this disease. Moreover, diseases where GABA neurons are still functioning, but at abnormally low levels, also lead to the postulation of a role for GABA in the etiology of CNS pathologies.

Under physiological conditions GABA does not significantly cross the blood-brain barrier. Thus, only at highly toxic doses was GABA shown in clinical studies to have a definite therapeutic action in epileptics, Tower, D. B., in *Nervous System Function:* 461, Roberts et al., editors, Raven Press, N.Y., (1976). Consequently, clinically useful GABA agonists or prodrugs with a capacity to cross the blood-brain barrier would have extreme therapeutic relevance for the treatment of these conditions. Such an approach requires that GABA receptors on post-synaptic sites remain intact following the degeneration of GABA neurons.

Along these lines, several attempts have been made to increase GABAergic activity in the brain by administration of GABA derivatives or analogues.

Research by Galzigna et al., *Arch. Int. Pharmacodyn.:* 235, 73 (1978), indicates that when the NH_2 function of GABA was blocked with either a benzoyl group, or a pivaloyl group, the resulting compounds were able to penetrate the blood-brain barrier when subcutaneously injected into rats.

Of the putative GABA mimetics which enter the brain, only muscimol has been widely examined, and even this compound enters the brain to a very limited extent, Maggi et al., *J. Neuropharmacology:* 18, 361 (1979). However, muscimol exhibits an unacceptable CNS toxicity, which prevents its wide clinical use.

Kaplan et al., *J. Med. Chem.:* 23, 702 (1980), have reported the use of derivatives where GABA is attached through an imine link (Schiff base) to a lipophilic carrier. The data show a reversal of bicuculline-induced lethality and convulsions indicating that these compounds can cross the blood-brain barrier of the rat.

Krogsgaard-Larsen, *J. Med. Chem.:* 24 (12), 1377 (1981), reviewed the use of GABA agonists, antagonists and uptake inhibitors. Baclofen and cyclic GABA structures such as muscimol and its derivatives, Kojic amine, isoguvacine, nipecotic acid and its derivatives, among others are analyzed, as well as their pharmacological activities in a variety of disorders. Of all the compounds analyzed, tetrahydroisoxazolopyridine-3-ol (THIP) penetrates the blood-brain barrier without being peripherally degraded.

Frey et al., *Neuropharmacology:* 19, 217 (1980), have shown that cetyl GABA has low anticonvulsant activity at dosages of 10–25 mg per kg when given intraperitoneally to mice and up to 100 mg per kg when given orally. The anticonvulsant effect was demonstrable only by threshold determinations, but there was substantially no protection against seizures elicited by high doses of penetrazole or by the maximal electroshock, and, in both cases, there was substantially no effect on the extensor phase of the penetrazole convulsion. In addition to this low protection against convulsions and seizures, cetyl GABA was also shown to only slightly increase GABA levels in brain, thus suggesting that cetyl GABA may not reach the brain in substantially sufficient amounts. In addition, cetyl GABA was fairly toxic when given intravenously and intraperitoneally.

Thus, a number of agents having sufficient pharmacological activity have been tested, either as GABA agonists or antagonists, or for their ability to release GABA from the CNS neurons. At best, these approaches have resulted in a trade off between improvement of transport across the blood-brain barrier, and the worsening of side effects. Accordingly, new compounds capable of crossing the blood-brain barrier are needed.

Other GABA esters are also known in the prior art.

Jones, U.S. Pat. No. 4,316,892, reported derivatives of N-enkephalin GABA to be useful as analgesics when administered orally in dosages of 0.5 to 5 mg per kg of body weight. These compounds include the free acid, lower alkyl esters, or aklylamide derivatives.

Somatostatin-GABA cyclic peptide derivatives having peripheral somatostatin-like activities have been reported by Rink et al., in U.S. Pat. No. 4,328,214. These derivatives have a strong inhibiting effect on the insulin and glucagon secretion of the pancreas, and are therefore useful in the treatment of diabetes or blood losses in the gastrointestinal tract. Cyclic peptide deriv-